NTP
National Toxicology Program

Implementation of Workshops and Retreat Recommendations

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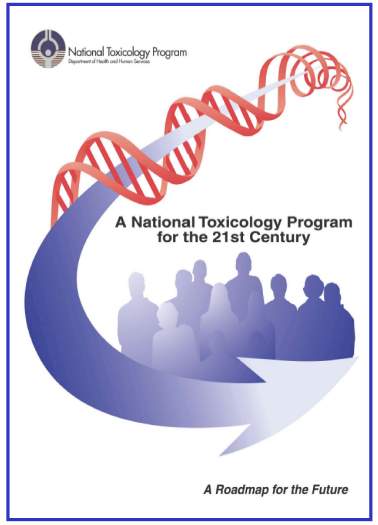
New Opportunities and Directions

Realignment provides a structure to 1) substantially increase efficiency and 2) afford opportunities for fresh leadership and new approaches

- Incorporate the Laboratory of Experimental Pathology
  - Create a Cellular and Molecular Pathology Branch- Dr. Robert Sills, Branch Chief
- Implement a program in host susceptibility
  - Create a Host Susceptibility Branch
- Reinvigorate toxicology
  - Create a Toxicology Branch
- Integrate chemistry, ADME, Project Officers and information systems
  - Create a Program Operations Branch
- Implement the Roadmap
  - Create a Bio-molecular Screening Branch



NTP Testing Strategies

- Strains and stocks: Should we switch? A workshop
  - June 16-17, 2005 at NIEHS
  - Evaluate current rodent models and multiple strain approach for chronic bioassay
  - Overall recommendations:
    - Discontinue use of NTP F344/N rat; establish new F344 line
    - Continue use of B6C3F1 mouse; sequence parental strains
    - Multiple strain approach is a viable option for cancer hazard identification; no overall recommendation on use
  - King-Herbert, A, Thayer, K, (2006) *Toxicol. Pathol*. 34:802-805

Strains and Stocks Workshop- Rat Group

- Some support for outbred strains because of
  - Little data on inbreds other than the F344
  - Used by pharma and virtues of the Wistar
- Liabilities of the current F344/N sub-strain (breeding problems, seizures) suggest colony should be discontinued
- Consider F1 hybrid with Brown-Norway
- Do not use additional single or multiple strains of rats
- If a new strain is chosen it becomes the default strain for all studies unless factors (metabolism) indicate otherwise

Strains and Stocks Workshop- Mouse Group

- Use isogenic strains to minimize genetic drift
- F1 hybrids preferable to inbreds
- Liver tumor incidence in B6C3F1 not yet critical
- Continued use of the mouse is essential in cancer screening
  - Allows identification of multiple species carcinogens
  - Allows utilization of extensive genetic information on mice
- If additional, or multiple strain approach is selected:
  - Add one at a time to cancer studies while keeping the B6C3F1
  - Choose a fixed set of strains, from those being re-sequenced
  - Choose parental strains genetically distant from one another

Strains and Stocks Workshop- Multiple Strain Group

- Multiple strain approach is a viable option because:
  - Captures genetic variation
  - Sufficient statistical power using current numbers to identify strong heterogeneous response
  - Could help identify mechanisms
- Liabilities of the approach include:
  - Added cost for range finding studies
  - Increased animal resource costs
  - Need for historical data
  - Regulatory acceptance is questionable- pooled vs separate strain analysis
  - Currently little information available to guide strain selection

Hormonally-induced Reproductive Tumors: Relevance of Rodent Bioassays

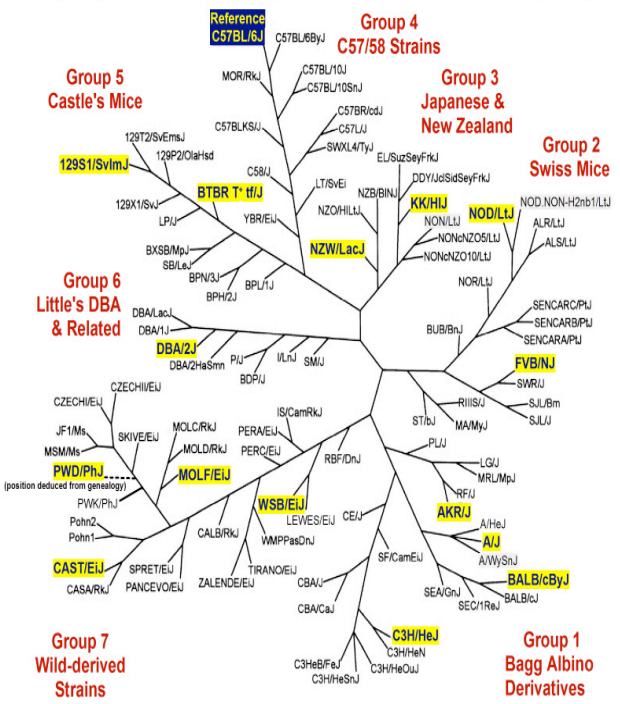
- May 2006, Raleigh, NC
  - Discuss the adequacy and relevance to human disease outcome of rodent models for four types of hormonally induced tumors
    - Breast, ovary, prostate, and testis
  - Recommendations:
    - Utilize alternative models
    - Utilize additional endocrine responsive endpoints in pre-chronic studies
    - Discontinue use of F344/N rat
    - Recognize importance of developmental programming
  - Thayer, KA, Foster, PM (2007) *Environ. Health Perspect*. 115:1351-1356.

Biomarkers for Toxicology Studies

- September 20-21, 2006, NIEHS
  - Identify biomarkers for lung, cardiovascular system, and carbohydrate and lipid metabolism to include in NTP pre-chronic studies
    - Added troponin T to pre-chronic studies at days 3, 21 and 90
    - Added cholesterol and triglycerides to clinical pathology battery
    - Fructosamine (glycated albumin) under consideration
    - Panel of inflammation markers also under consideration
  - Dunnick, JK, Thayer, KA and Travlos, GS (2007) *Toxicol. Sci*.100:29-35.

Program Changes in Response to Workshops and NTP Staff Retreat

- Maintain use of B6C3F1 hybrid mouse
  - Hybrid favored
  - Parental strains genetically diverse
- Discontinue use of F344 rat- select Wistar Han
  - Low incidence of most spontaneous tumors
  - Long lifespan
  - Moderate size
  - Robust reproductive capacity
  - Adequate commercial availability- good colony management



Program Changes in Response to Workshops and NTP Staff Retreat (cont'd)

- Reconsider young adult rodent as default model
  - Contract capabilities in reproductive toxicology have been restored
  - Hormonal workshop recommendation
  - Increased emphasis on children's environmental health and regulations
  - Focus on rat for increased consideration for perinatal dosing
  - Development of study design for in utero, lactational exposure

Program Changes in Response to Workshops and NTP Staff Retreat (cont'd)

- Changes to pathology processes
  - Engage staff pathologists earlier in the pathology review process
  - Explore the feasibility of virtual PWGs
  - Develop SOPs for pathology reviews for immunotoxicity and developmental toxicity studies
  - Initiate a newsletter on organ specific diagnostic criteria
  - Streamline some steps in the pathology materials audit process based on experience and history
  - Incorporate clinical pathology recommendations from Biomarkers Workshop